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| <b>(54) Title:</b> QUINUCLIDINE DERIVATIVES AS SUBSTANCE P ANTAGONISTS<br><br><b>(57) Abstract</b><br><p>A series of <i>cis</i>-3-[(cyclic)methylamino]-2-[(<math>\alpha</math>-substituted)phenylmethyl]quinuclidines, 3-[(cyclic)methylimino]-2-[(<math>\alpha</math>-substituted)-phenylmethyl]quinuclidines and <i>cis</i>-3-[(cyclic)-methylenamino]-2-[(<math>\alpha</math>-substituted)phenylmethyl]-quinuclidines, including their pharmaceutically acceptable salts, are disclosed. These particular compounds are found to be useful as substance P antagonists and therefore, are of value in treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. Preferred member compounds include <i>cis</i>-3-[(2-chlorophenyl)methylamino]-2-benzhydryl-quinuclidine, <i>cis</i>-3-[(2-trifluorophenyl)methylamino]-2-benzhydryl-quinuclidine and <i>cis</i>-[(2-methoxyphenyl)methylamino]-2-benzhydrylquinuclidine. Methods for preparing these compounds from known starting materials are provided.</p> |           |  |

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QUINUCLIDINE DERIVATIVES AS SUBSTANCE P ANTAGONISTSTechnical Field

This invention relates to new and useful quinuclidine derivatives of interest to those in the field of medicinal chemistry and chemotherapy. More particularly, it is concerned with a novel series of

5 cis-3-[(cyclic)methylamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidines, 3-[(cyclic)methylimino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidines and cis-3-[(cyclic)methyleneamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidines, including their pharmaceutically

10 acceptable salts, which are of especial value in view of their ability to antagonize substance P. In this way, these compounds are of use in treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. The

15 invention also includes a new method of therapy within its scope.

Background Art

E. J. Warawa in U.S. Patent No. 3,560,510 discloses certain 3-amino-2-benzhydrylquinuclidines as

20 being useful as diuretic agents, with the corresponding unsubstituted 3-benzylamino compounds acting as intermediates for same. Additionally, E. J. Warawa et al. in the Journal of Medicinal Chemistry, Vol. 18, p. 587 (1975) extends this work to other members of the

25 series wherein the 3-amino moiety is either ethylamino,  $\beta$ -phenylethylamino,  $\beta$ -isopropylamino or 2-furfurylamino, but in no instance is there any substitution on the phenyl group itself and the 2-benzhydryl moiety is always symmetrically substituted (or unsubstituted).

Furthermore, neither of the aforementioned documents teaches or suggests any of these compounds to be useful as substance P antagonists.

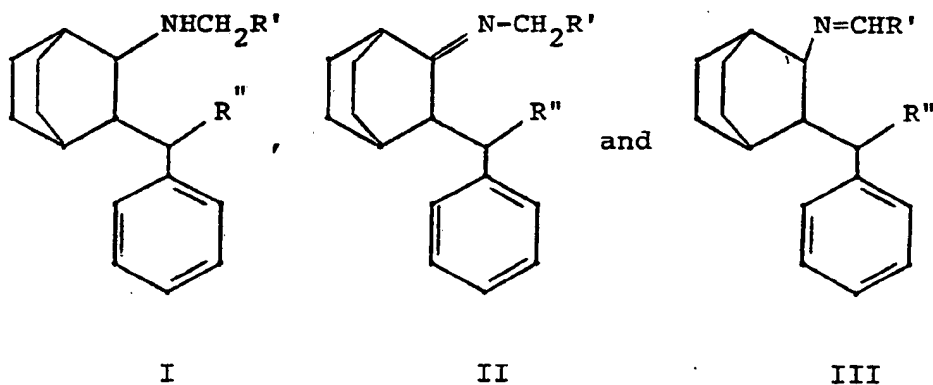
Substance P is a naturally occurring undecapeptide  
5 belonging to the tachykinin family of peptides, the  
latter being so-named because of their prompt  
stimulatory action on smooth muscle tissue. More  
specifically, substance P is a pharmacologically-active  
neuropeptide that is produced in mammals (having  
10 originally been isolated from gut) and possesses a  
characteristic amino acid sequence that is illustrated  
by D. F. Veber et al. in U.S. Patent No. 4,680,283.  
The wide involvement of substance P and other  
tachykinins in the pathophysiology of numerous diseases  
15 has been amply demonstrated in the art. For instance,  
substance P has recently been shown to be involved in  
the transmission of pain or migraine [see B.E.B.  
Sandberg et al., Journal of Medicinal Chemistry, Vol.  
25, p. 1009 (1982)], as well as in central nervous  
20 system disorders such as anxiety and schizophrenia, in  
respiratory and inflammatory diseases such as asthma  
and rheumatoid arthritis, respectively, and in  
gastrointestinal disorders and diseases of the GI  
tract, like ulcerative colitis and Crohn's disease,  
25 etc. (see D. Regoli in "Trends in Cluster Headache,"  
Edited by F. Sicuteri et al., Elsevier Scientific  
Publishers, Amsterdam, 1987, pp. 85-95).

In the recent past, some attempts have been made  
to provide antagonists for substance P and other  
30 tachykinin peptides in order to more effectively treat  
the various disorders and diseases listed above. The  
few such antagonists thus far described are all  
peptide-like in nature and are therefore too labile  
from a metabolic point of view to serve as practical  
35 therapeutic agents in the treatment of disease. The

non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the previously-discussed prior art agents.

## Disclosure of the Invention

In accordance with the present invention, it has now been surprisingly found that various novel cis-3-methylamino-2-[( $\alpha$ -substituted)phenylmethylamino]-quinuclidine compounds, as well as the corresponding 3-methylimino and cis-3-methyleneamino analogs, are useful when employed in therapy as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammalian subject so afflicted. More specifically, the novel compounds of this invention are all quinuclidine derivatives of the formulae:



and include the pharmaceutically acceptable salts thereof, wherein R' is cycloalkyl having from five to seven carbon atoms, norbornyl, pyrrolyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with up to two substituents selected from

fluorine, chlorine, bromine, trifluoromethyl, alkyl  
having from one to three carbons, alkoxy having from  
one to three carbon atoms, carboxy, alkoxycarbonyl  
having from one to three carbon atoms in the alkoxy  
moiety or benzyloxycarbonyl; and R" is branched chain  
alkyl having from three to four carbon atoms, branched  
chain alkenyl having from five to six carbon atoms,  
cycloalkyl having from five to seven carbon atoms,  
furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl  
optionally substituted with up to two substituents  
selected from fluorine, chlorine, bromine,  
trifluoromethyl, alkyl having from one to three carbon  
atoms, alkoxy having from one to three carbon atoms,  
carboxy, alkoxycarbonyl having from one to three carbon  
atoms in the alkoxy moiety or benzyloxycarbonyl, with  
the proviso that said R" is other than unsubstituted  
phenyl when said R' is unsubstituted phenyl, pyrrolyl  
or thienyl. These novel compounds are useful as  
substance P antagonists, i.e., they possess the ability  
to antagonize the effects of substance P at its  
receptor site in mammals, and therefore they are able  
to function as therapeutic agents in the treatment of  
the aforementioned disorders and diseases in an  
afflicted mammal. Additionally, the compounds of  
formulae II and III are also useful as intermediates  
for preparing the final products of formula I.

A preferred group of compounds of the present  
invention of particular interest is that of structural  
formulae II and III wherein R' is 2-chlorophenyl,  
2-trifluoromethylphenyl or 2-methoxyphenyl and R" is  
phenyl. Another group of preferred compounds of  
particular interest is that of structural formula I  
wherein R' is phenyl or 2-thienyl and R" is substituted  
phenyl; especially preferred compounds within the  
latter group include those wherein R" is  
3-methoxyphenyl or 4-methoxycarbonylphenyl. Still

another group of preferred compounds of the present invention of particular interest is that of structural formula I wherein R' is pyridyl, indolyl or substituted phenyl and R" is phenyl; especially preferred compounds within this group include those where R' is 4-pyridyl, 3-indolyl, fluorophenyl, difluorophenyl, chlorophenyl, trifluoromethylphenyl, C<sub>1</sub>-C<sub>3</sub> alkylphenyl such as 4-methylphenyl, C<sub>1</sub>-C<sub>3</sub> alkoxyphenyl such as methoxyphenyl, and C<sub>1</sub>-C<sub>3</sub> alkoxycarbonylphenyl such as 4-methoxycarbonylphenyl. The preferred configuration for compounds of structural formulae I and III is cis with respect to the substituents located at the 2- and 3-positions of the quinuclidine nucleus.

Of especial interest in this connection are such typical and preferred member compounds of the invention as cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine, cis-3-[(2-trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine and cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydrylquinuclidine, and their pharmaceutically acceptable acid addition salts. These key compounds are all potent substance P antagonists and therefore of value when employed in therapy for the various reasons previously discussed.

There is also included within the purview of this invention various novel pharmaceutical compositions useful for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment, comprising a pharmaceutically acceptable carrier or diluent and a therapeutically-effective amount of a compound selected from the group of quinuclidine derivatives having the formula I, II or III, or a pharmaceutically salt thereof, wherein R' and R" are each as previously defined, with the proviso that said R" is other than unsubstituted phenyl when

said R' is unsubstituted phenyl, pyrrolyl or thienyl. Additionally, there is also meant to be included pharmaceutical compositions of the same type wherein the active ingredient, as previously defined, is present in an amount that is effective for antagonizing the effects of substance P at its receptor site in said mammal.

There is also further included within the purview of this invention a method of treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment, which comprises administering to said mammal a therapeutically-effective amount of a compound selected from the group of quinuclidine derivatives having the formula I, II or III, or a pharmaceutically acceptable salt thereof, wherein R' and R" are each as previously defined, but without the aforesaid proviso. Additionally, there is also included within the purview of the invention a method for antagonizing the effects of substance P at its receptor site in a mammal in need of such treatment, which comprises administering to said mammal a compound selected from the group of quinuclidine derivatives having the formula I, II or III, or a pharmaceutically acceptable salt thereof, but without the aforesaid proviso, in an amount that is effective for antagonizing the effects of substance P at its receptor site in said mammal. Thus, the novel method of treatment aspect of the present invention necessarily encompasses the use of both old and new compounds for the present purposes at hand, inasmuch as it additionally includes the new use of known compounds of structural formulae I, II and III wherein R' is unsubstituted phenyl, 2-pyrrolyl or 2-thienyl and R" is



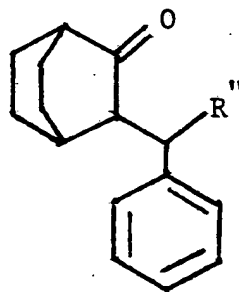
also unsubstituted phenyl.

#### Detailed Description

In accordance with the process employed for preparing the novel cis-3-[(cyclic)methylamino-2-  
5 [( $\alpha$ -substituted)-phenylmethyl]quinuclidine compounds of formula I of this particular invention, a 3-[(cyclic)-methylimino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compound of the formula II or a cis-3-[(cyclic)-methyleneamino-2-[( $\alpha$ -substituted)phenylmethyl]quinu-  
10 clidine compound of the formula III, wherein R' and R" are each as previously defined with the aforesaid proviso, is subjected to the selective reducing action of a suitable metallo reducing agent such as a metal hydride like a borane hydride, alane hydride or a metal  
15 hydride complex like lithium aluminum hydride or sodium borohydride, or an organo-metallic complex such as boron-methyl sulfide, 9-borabicyclononane (9-BBN) and the like. In general, the reduction step is carried out in a reaction-inert polar or non-polar  
20 aprotic organic solvent at a temperature that is in the range of from about 0°C. up to about 120°C. until the reduction step to form the desired cis-3-[(cyclic)-methylamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine final product is substantially complete.  
25 The preferred reaction temperature for the reduction step is often at the lower end of the aforesaid range, e.g., at about 15-40°C., with a temperature at or near room temperature (ca. 20°C.) usually being most preferred. The reaction pressure is not critical,  
30 e.g., a reaction pressure of about 0.5 to about 2.0 atmospheres is generally employed, with the preferred pressure usually being at or near ambient pressure (i.e., at about one atmosphere). Preferred aprotic

solvents for use in this connection include acetonitrile, dimethylformamide, diethylformamide, dimethylacetamide, benzene and ethers like diethyl ether, di-isopropyl ether, di-n-butyl ether, tetrahydrofuran, dioxane and 1,2-dimethoxyethane (glyme) and dimethylcellosolve. A preferred embodiment involves the use of 9-borabicyclononane as the reducing agent in an ethereal solvent medium, such a cyclic ether like tetrahydrofuran or dioxane, or a glycol-derived ether like 1,2-dimethoxyethane at a temperature ranging from about room temperature (ca. 20°C.) up to the reflux temperature of the reaction mixture. In this way, the desired cis-isomer of the final product is produced with a high degree of selectivity. Upon completion of the reduction step, the desired methylamine final product is readily recovered from the reaction mixture by any number of conventional procedures well-known to those skilled in the art.

The novel 3-[(cyclic)methylimino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compounds of formula II, which are required for preparing the novel final products of formula I, are also useful as substance P antagonists. They are, in turn, prepared by condensing a corresponding 2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine-3-one compound of the formula IV:



IV

wherein R" is defined as aforesaid, with a (cyclic)methylamine of the formula  $R'CH_2NH_2$ , wherein R' is also defined as before, to form the desired imine final product of structural formula II. This

5 particular reaction is normally carried out by heating the two reactants together at a elevated temperature in a reaction-inert organic solvent, such as an aromatic hydrocarbon solvent like benzene, toluene and xylene, and preferably in the presence of a catalytic amount of

10 a suitable acidic condensing agent like p-toluene-sulfonic acid or camphorsulfonic acid, such that the water formed as a byproduct in the reaction is thereafter immediately collected as it distills over at the boiling point of the solvent. Alternatively, the

15 reaction can also be carried out by using a dehydrating agent like titanium tetrachloride in a suitable reaction-inert organic solvent, such as a cyclic ether like tetrahydrofuran or dioxane. In general, the reaction is conducted at a temperature that is in the

20 range of from about 35°C. up to about 140°C. and preferably at about 65-110°C. until the condensation is substantially complete, i.e., until no more water of reaction forms, and this will usually require a period of at least about one hour and preferably up to about

25 18-24 hours for the present purposes at hand. Although substantially equimolar proportions of reactants are normally required, it is preferable in practice to employ an excess of the (cyclic)methylamine base, e.g., up to about 2.0 mole of amine per mole of 2-[( $\alpha$ -

30 substituted)phenylmethyl]quinuclidin-3-one starting material, in order to ensure completeness of reaction without causing unwanted side reactions to occur to any significant degree. Upon completion of the reaction, the desired methylimine final product is then easily

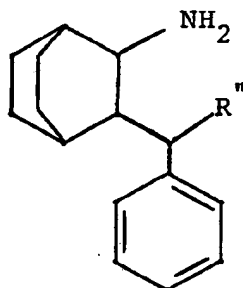
35 isolated from the reaction mixture in a conventional

manner; e.g., by first concentrating said mixture in vacuo and thereafter triturating the residue with a suitable solvent such as isopropanol, followed by recrystallization from the same solvent or tetrahydrofuran if necessary, or else used as such in the next and final reduction step to afford the desired methylamine final product without any further purification first being employed.

The starting materials required for preparing the novel 3-[(cyclic)methylimino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine formula II compounds of this invention are either known compounds which are readily available commercially like many of the amines of formula  $R'CH_2NH_2$  (e.g., benzylamine or cyclohexylamine, etc.), or they are described in the literature like 2-benzhydrylquinuclidin-3-one (see E. J. Warawa in U.S. Patent No. 3,560,510), or else they can easily be synthesized by those skilled in the art starting from common chemical reagents and using conventional methods of organic synthesis. For instance, the 2-[( $\alpha$ -substituted)phenylmethyl]quinuclidin-3-one compounds are readily prepared from the known quinuclidin-3-one [C. R. Clemons et al., in the Journal of the Chemical Society (London), p. 1241 (1939)] via a two-step reaction sequence involving (1) condensation with an appropriate aldehyde compound of the formula  $R''CHO$  to form the corresponding 2-( $\alpha$ -substituted)methylidenequinuclidin-3-one, followed by (2) treatment of the latter intermediate with phenylmagnesium bromide in a Grignard reaction to yield the desired 2-[( $\alpha$ -substituted)phenylmethyl]quinuclidin-3-one starting material (e.g., see Preparations A-C in this regard).

The novel cis-3-[(cyclic)methyleneamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compounds of formula III, which are also used to prepare the novel

final products of formula I and are also additionally useful as substance P antagonists, are prepared by condensing a corresponding 3-amino-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compound of the formula V:



V

wherein  $\text{R}''$  is defined as aforesaid, with an appropriate cyclic aldehyde compound of the formula  $\text{R}'\text{CHO}$ , wherein  $\text{R}'$  is also defined as before, to form the desired methyleneamine final product of structural formula III.

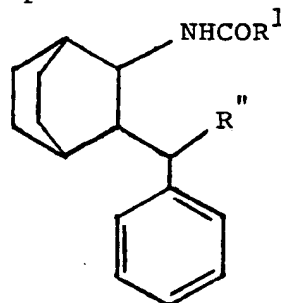
10 This particular reaction is normally carried out in the same manner as that described previously for the condensation reaction between the quinuclidin-3-ones of formula IV and the amines of formula  $\text{R}'\text{CH}_2\text{NH}_2$  to form the imines of formula II, except that in the present  
15 instance it is preferable to employ an excess of the  $\text{R}'\text{CHO}$  aldehyde reagent rather than the 3-amino base compound, in order to ensure completeness of reaction with little or no byproduct formation that could possibly contaminate the desired final product of  
20 structural formula III. In practice, it has been found most convenient to use up to about 3.0-6.0 mole of cyclic aldehyde per mole of 3-amino-2-[( $\alpha$ -substituted)-phenylmethyl]quinuclidine starting material for the present purposes at hand. Upon completion of the  
25 reaction, the desired methyleneamine final product is either isolated and purified as such in the same manner

as that described previously for the corresponding methylimine compound, or else used as the key substrate without any further purification in the next and final reduction step to form the desired methylamine final product of structural formula I.

The starting materials required for preparing the novel cis-3-[(cyclic)methyleneamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compounds of formula III are either known compounds which are readily available commercially like many of the aldehydes of formula R'CHO (e.g., 2,6-dichlorobenzaldehyde), or they are described in the literature like 3-amino-2-benzhydrylquinuclidine [E. J. Warawa et al., in the Journal of Medicinal Chemistry, Vol. 18, p. 587 (1975)], or else they can easily be synthesized by those skilled in the art starting from common chemical reagents and using conventional methods of organic synthesis. For instance, the 3-amino-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine compounds are readily prepared from the corresponding 3-benzylamino compounds of formula I by treating the latter type compounds with ammonium formate in the presence of a noble metal catalyst, such as palladium-on-carbon (preferably about 10% by weight), in a reaction-inert organic solvent, such as a lower alkanol like methanol, ethanol or isopropanol, at a temperature ranging from about 20°C. up to about 100°C. and preferably at the reflux temperature of the reaction mixture.

Additionally, the cis-3-[(cyclic)methylamino]-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidine final products of formula I can also be prepared by another alternate route which involves subjecting a corresponding 3-[(cyclic)carbonylamino]-2-[( $\alpha$ -substituted)phenyl-

methyl]quinuclidine compound of the formula:



VI

to the selective reducing action of a suitable metallo  
reducing agent such as a metal hydride like a borane  
hydride, alane hydride or hydride complex like lithium  
5 aluminum hydride, or an organo-metallic complex such as  
boron-methyl sulfide and the like. This particular  
reaction is normally carried out in the same manner as  
that described previously for the reduction of the  
corresponding formula II methylimines and the formula  
10 III methyleneamine compounds to form the methylamine  
final products of formula I, except that in the present  
case the reaction temperature is usually in the range  
of from about 20°C. up to about 120°C., with the  
preferred temperature often being found in the  
15 neighborhood of the near upper end of the aforesaid  
range, e.g., at about 65-100°C., with a temperature at  
or near the reflux temperature of the reaction mixture  
usually being most preferred. Upon completion of the  
reduction reaction, the desired methylamine final  
20 product of formula I is readily recovered from the  
reaction mixture in essentially the same manner as  
before.

The 3-[(cyclic)carbonylamino]-2-[( $\alpha$ -substituted)  
phenylmethyl]quinuclidines of formula VI, which are  
25 required as starting materials for preparing the novel  
final products of formula I, are, in turn, prepared

from the previously-discussed corresponding 3-amino-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidines of formula V by reacting same with an activated derivative of a known carboxylic acid of the formula R'COOH. This is readily accomplished by first activating said acid compound of formula R'COOH by converting it into a derivative such as the acid chloride, the acyl imidazole or the acyl azide, using conventional methods or organic synthesis well-known to those skilled in the art. For example, the acid can be first reacted in a reaction-inert organic solvent, such as dioxane tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane-(glyme) or methylene chloride, with an activating agent such as thionyl chloride, carbonyl di-imidazole or diphenyl phosphoryl azide, as the case may be, optionally in the presence of an organic base such as triethylamine, at a temperature ranging from ambient (ca. 20°C.) to the reflux temperature of the reaction mixture (e.g., at about 20-80°C.), with the preferred reaction temperature being in the neighborhood of the lower limit of the aforesaid range (e.g., at about 20-35°C.). Upon completion of this particular reaction step, the compound of formula V is next added to the mixture and the reaction continued at a temperature of from about 65°C. up to about 100°C., and preferably at the reflux temperature of mixture, until the production of the desired 3-(cyclic)carbonylamino derivative is substantially complete (and this will usually require a period of at least about one-half hour and sometimes up to as long as 24 hours). At this point, the desired 3-(cyclic)carbonylamino derivative is readily recovered from the reaction mixture in a conventional manner and thereafter reduced to the corresponding 3-(cyclic)-methylamine compound, i.e., the methylamine final



product of formula I, in the manner previously described.

Insofar as the majority of the 3-methylamino-2-  
[( $\alpha$ -substituted)phenylmethyl]quinuclidine compounds of  
5 formula I of this invention are basic compounds, as are  
the corresponding methylimines and methyleneamines of  
formulas II and III, they are all capable of forming a  
wide variety of different salts with various inorganic  
and organic acids. Although such salts must be  
10 pharmaceutically acceptable for administration to  
animals, it is often desirable in practice to initially  
isolate the quinuclidine base compound from the  
reaction mixture as a pharmaceutically unacceptable  
salt and then simply convert the latter back to the  
15 free base compound by treatment with an alkaline  
reagent and thereafter, subsequently convert the latter  
free base to a pharmaceutically acceptable acid  
addition salt. The acid addition salts of the  
quinuclidine base compounds of this invention are  
20 readily prepared by treating the base compound with a  
substantially equivalent amount of the chosen mineral  
or organic acid in an aqueous solvent medium or in a  
suitable organic solvent, such as methanol or ethanol.  
Upon careful evaporation of the solvent, the desired  
25 solid salt is readily obtained.

The acids which are used to prepare the  
pharmaceutically acceptable acid addition salts of the  
aforementioned quinuclidine base compounds of this  
invention are those which form non-toxic acid addition  
30 salts, i.e., salts containing pharmacologically  
acceptable anions, such as the hydrochloride,  
hydrobromide, hydroiodide, nitrate, sulfate or  
bisulfate, phosphate or acid phosphate, acetate,  
lactate, citrate or acid citrate, tartrate or  
35 bitartrate, succinate, maleate, fumarate, gluconate,

saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

5        Those quinuclidine compounds of the invention which are also acidic in nature, e.g., where R" is carboxyphenyl, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or  
10       alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which  
15       form non-toxic base salts with the herein described acidic quinuclidine derivatives. These particular non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can  
20       easily be prepared by treating the aforementioned acidic quinuclidine compounds with an aqueous solution containing the desired pharmacologically acceptable cation, and then evaporating the resulting solution to dryness, preferably under reduced pressure.  
25       Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric  
30       quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum production of yields of the desired final product.

35       The quinuclidine compounds of the present invention of formulas I, II and III exhibit significant substance P receptor-binding activity and therefore,

are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of said substance P activity. Such conditions include gastrointestinal disorders such as ulcer and colitis and other like diseases of the gastrointestinal tract, central nervous system disorders such as anxiety and psychosis, inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases, respiratory diseases such as asthma, as well as pain in any of the aforesaid conditions, including migraine. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans. For instance, cis-3-[(2-chloro-phenyl)methylamino]-2-benzhydrylquinuclidine, a preferred compound of the present invention, when tested as an anti-inflammatory agent exhibits a significant degree of activity in the standard carrageenin-induced rat foot edema test [described by C. A. Winter et al., Proceedings of the Society of Experimental Biology and Medicine, Vol. 111, p. 544 (1962)], where it was found to cause a 50% inhibition in swelling at the 100 mg./kg. dose level when given by the oral route. Moreover, when tested as an anti-psychotic agent, this same compound was found to produce a 50% inhibition of substance P-induced locomotion in rats at the 32 mg./kg. dose level when given by the intraperitoneal route.

The quinuclidine compounds of the present invention can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in doses ranging from about 5.0 mg. up to about 1500 mg. per day, although variations will necessarily occur

depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from about 0.07 mg. to about 21 mg. per kg. of body weight per day is most desirably employed.

Nevertheless, variations may still occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers,

sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous

solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention, as substance P antagonists, is determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonist activity of the herein described quinuclidine compounds is evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic  $IC_{50}$  values for each compound tested.

The anti-inflammatory activity of the compounds of the present invention is demonstrated in the previously mentioned standard carrageenin-induced rat foot edema

test. In this test, anti-inflammatory activity is determined as the percent inhibition of edema formation in the hind paw of male albino rats (weighing 150-190 g.) in response to a sub-plantar injection of carrageenin. The carrageenin is injected as a 1% aqueous solution. Edema formation is then assessed by measuring the volume of the injected paw initially as well as three hours after the carrageenin injection. The increase in volume three hours after carrageenin injection constitutes the individual response. Compounds are considered active if the difference in response between the drug-treated animals (six rats/group) and a control group receiving the vehicle alone is significant on comparison with the results afforded by a standard compound like phenylbutazone at 33 mg./kg., via the oral route of administration.

The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced hypermotility in rats. This study is carried out by first dosing the rats with a control compound or with an appropriate test compound of the present invention, then injecting the rats with substance P by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimuli.

#### PREPARATION A

In a 50 ml. round-bottomed reaction flask equipped with reflux condenser and nitrogen-inlet tube, there were placed 5.28 g. (0.04258 mole) of quinuclidin-3-

one [C. R. Clemo et al., in the Journal of the Chemical Society (London), p. 1241 [1939], 11.18 g. (0.06387 mole) of 2,4-dichlorobenzaldehyde, 340 mg. (0.00852 mole) of sodium hydroxide and 21 ml. of ethanol. The resulting reaction mixture was next refluxed for a period of 40 minutes, then cooled to ambient temperatures and the precipitated product subsequently recovered by means of suction filtration. After washing the latter material with ethanol and vacuum drying to constant weight, there were ultimately obtained 8.71 g. (70%) of pure 2,4-dichlorobenzylidene-quinuclidin-3-one in the form of a yellow solid melting at 117-119°C.; IR (cm.<sup>-1</sup>, KBr) 1710, 1700 (C=O). The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data.

Mass Spectrum (%): 281/283/285 (parent, 2.5 for 281), 248(34), 246(78), 220(26), 218(100), 192(25), 190(60), 186(27), 184(40), 172(25), 164(24), 162(24), 149(24), 136(26), 135(24), 172(32), 126(24), 123(26), 114(26), 99(26), 55(40), 53(22).

NMR Data: <sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>) 1.9-2.0(m, 4H), 2.49(m, 1H), 2.8-3.2(m, 4H), 7.1-7.3 and 8.4-8.5(m, 3H).

#### PREPARATION B

In a 250 ml. round-bottomed reaction flask equipped with magnetic stirring bar and nitrogen-inlet tube, there were placed 15 ml. (0.04575 mole) of a 1.5 M solution of phenylmagnesium bromide in diethyl ether and 76 ml. of dry toluene. Stirring was commenced and the solution was cooled to 0°C., while 8.57 g. (0.03049 mole) of 2,4-dichlorobenzylidenequinuclidin-3-one (the product of Preparation A) in 10 ml. of toluene were added thereto in a dropwise manner. The reaction mixture was then warmed to room temperature (ca. 20°C.) and allowed to stir for a period of 14 hours before finally being quenched with aqueous ammonium chloride.



This resulted in the formation of two layers which were then separated, and the separated aqueous layer was next extracted with fresh methylene chloride. The resulting organic layers were then combined and subsequently dried over anhydrous sodium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a solid residual product which subsequently crystallized from ethanol to afford 6.70 g. (61%) of pure 2-[(2,4-dichlorophenyl)phenylmethyl]quinuclidin-3-one in the form of a white solid melting at 144-152°C.; IR(cm.<sup>-1</sup>, KBr), 1725(C=O). The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data.

Mass Spectrum (%): 360/362/364 (parent, 1.5 for 360), 333(24), 331(27), 292(22), 290(33), 227(26), 214(26), 199(23), 178(64), 177(22), 176(26), 172(43), 165(72), 164(23), 161(56), 159(84), 131(30), 130(34), 91(100), 77(29), 68(22), 55(54).

NMR Data: <sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>) 1.9-2.1(m, 4H), 2.44(m, 1H), 2.6-2.8(m, 2H), 2.9-3.1(m, 2H), 3.85(d, 1H), 5.12(d, 1H), 7.1-7.4(m, 8H).

#### PREPARATION C

The reaction procedures described in Preparations A-B are repeated to prepare the following 2[( $\alpha$ -substituted)phenylmethyl]quinuclidin-3-one compounds, starting from quinuclidin-3-one and the requisite organic aldehyde and proceeding thru the corresponding 2-[( $\alpha$ -substituted)benzylidene]quinuclidin-3-one intermediate in every instance, using the same molar proportions as before:

2-[(3-methoxyphenyl)phenylmethyl]quinuclidin-3-one

2-[(3-methoxycarbonylphenyl)phenylmethyl]quinuclidin-3-one

- 2-[(2,3-dichlorophenyl)phenylmethyl]quinuclidin-3-one  
2-[(2,4-difluorophenyl)phenylmethyl]quinuclidin-3-one  
2-[(3-trifluoromethylphenyl)phenylmethyl]quinu-  
clidin-3-one  
5 2-[(2-furyl)phenylmethyl]quinuclidin-3-one  
2-[(3,4-dichlorophenyl)phenylmethyl]quinuclidin-3-one  
2-[(4-pyridyl)phenylmethyl]quinuclidin-3-one  
2-[(E- and Z-2-tert.-butylvinyl)phenylmethyl]quinu-  
clidin-3-one  
10 2-[(2-methoxyphenyl)phenylmethyl]quinuclidin-3-one  
2-[(2-n-propylphenyl)phenylmethyl]quinuclidin-3-one  
2-[(4-carboxyphenyl)phenylmethyl]quinuclidin-3-one  
2-[(2-thienyl)phenylmethyl]quinuclidin-3-one  
2-[(2-biphenyl)phenylmethyl]quinuclidin-3-one  
15 2-[(3-pyridyl)phenylmethyl]quinuclidin-3-one  
2-[(cyclohexyl)phenylmethyl]quinuclidin-3-one.

#### PREPARATION D

In a 50 ml. round-bottomed reaction flask equipped  
with reflux condenser, magnetic stirring bar and  
20 nitrogen-inlet tube, there were placed 805.9 mg.  
(0.005757 mole) of 2-norbornanecarboxylic acid, 932.6  
mg. (0.005757 mole) of carbonyldiimidazole and 19 ml.  
of dry tetrahydrofuran. The reaction mixture was next  
25 stirred at room temperature (ca. 20°C.) for a period of  
30 minutes, followed by the addition thereto of 1.1207  
g. (0.003838 mole) of 3-amino-2-benzhydrylquinuclidine  
[E. J. Warawa et al., in the Journal of Medicinal  
Chemistry, Vol. 18, p. 71 (1975)]. The resulting  
mixture was then refluxed for a period of 18 hours,  
30 cooled to ambient temperatures and thereafter  
partitioned between water and methylene chloride. The  
separated organic layer was next washed with brine and  
then dried over anhydrous sodium sulfate. After  
removal of the drying agent by means of filtration and  
35 the solvent by means of evaporation under reduced

pressure, there was finally obtained a solid residual product which subsequently crystallized from isopropanol to yield 963 mg. (61%) of pure cis-3-(2-norbornylcarbonylamino)-2-benzhydrylquinuclidine in the form of a white solid melting at 203-207°C.; IR( $\text{cm}^{-1}$ , KBr), 1645(C=O). The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data, in addition to elemental analysis.

Mass Spectrum (%): 414(29, parent), 291(23), 248(31), 247(100), 181(28), 180(96), 167(22), 165(20), 125(28), 97(30), 96(25), 95(77), 91(34), 69(21), 67(26).

NMR Data:  $^1\text{H-NMR}(\delta, \text{CDCl}_3)$  0.8-3.1 (several multiplets, 19H), 3.94(m, 2H), 4.14(m, 1H), 4.35(m, 1H), 5.6-5.8(m, 1H), 7.0-7.4(m, 10H).

Anal. Calcd. for  $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O} \cdot 0.5\text{H}_2\text{O}$ : C, 79.39; H, 8.33; N, 6.61. Found: C, 79.33; H, 8.13; N, 6.72.

#### PREPARATION E

The procedure described in Preparation D was repeated to prepare the following cis-3-(homocyclic-carbonylamino)-2-benzhydrylquinuclidines, starting from the corresponding homocyclic-carboxylic acid and 3-amino-2-benzhydrylquinuclidine in each instance, and using the same molar proportions as before:

cis-3-(1-norbornylcarbonylamino)-2-benzhydrylquinuclidine, m.p. 220-230°C.

cis-3-(2-benzylphenylcarbonylamino)-2-benzhydrylquinuclidine, m.p. 215-222°C.

cis-3-(3,5-difluorophenylcarbonylamino)-2-benzhydrylquinuclidine, m.p. 225-230°C.

cis-3-(2,3-difluorophenylcarbonylamino)-2-benzhydrylquinuclidine, m.p. 250-256°C.

PREPARATION F

cis-3-Benzylamino-2-benzhydrylquinuclidine (m.p. 145-148°C.) was prepared according to the procedure described by E. J. Warawa et al., as first reported in the Journal of Medicinal Chemistry, Vol. 18, p. 587 (1975), wherein 3-keto-2-benzhydrylquinuclidine was condensed with benzylamine and the resultant intermediate, viz., 3-benzylimino-2-benzhydrylquinuclidine, was then reduced with sodium borohydride to afford the desired final product. The melting point of the final product was 151.5-152°C., according to E. J. Warawa et al.

PREPARATION G

cis-3-[(2-Thienyl)methylamino]-2-benzhydrylquinuclidine (m.p. 140-145°C.) was prepared in accordance with the procedure reported in Preparation F by condensing 3-keto-2-benzhydrylquinuclidine with (2-thienyl)methylamine (i.e., 2-thienylamine), followed by reduction of the resultant intermediate (viz., 3-[(2-thienyl)methylimino]-2-benzhydrylquinuclidine) with sodium borohydride to ultimately afford the desired final product.

PREPARATION H

cis-3-[(2-Pyrrolyl)methylamino]-2-benzhydrylquinuclidine (m.p. 137.5-138.5°C.) was prepared in accordance with the procedure reported in Preparation F by condensing 3-keto-2-benzhydrylquinuclidine with (2-pyrrolyl)methylamine, followed by reduction of the resultant intermediate (viz., 3-[(2-pyrrolyl)methylimino]-2-benzhydrylquinuclidine) with sodium borohydride to ultimately afford the desired final product.

EXAMPLE 1

A. In a 50 ml. round-bottomed reaction flask equipped with a Dean-Stark trap, reflux condenser and

nitrogen-inlet tube, there were placed 1.12 g. (0.00385 mole) of 3-keto-2-benzhydrylquinuclidine [E. J. Warawa et al., Journal of Medicinal Chemistry, Vol. 17, p. 497 (1974)], 652 mg. (0.00577 mole) of cyclohexylmethyl-  
5 amine, 17.8 mg. (0.00077 mole) of camphorsulfonic acid and 19 ml. of toluene. The reaction mixture was then refluxed azeotropically (with separation of water) for a period of 18 hours, cooled to ambient temperatures and concentrated in vacuo to afford a solid residue.

10 B. The residual material obtained above [crude 3-(cyclohexylmethylimino)-2-benzhydrylquinuclidine] was then dissolved in 13 ml. of dry tetrahydrofuran, and the resulting solution was cooled to 0°C., with stirring, while under a dry nitrogen atmosphere. At  
15 this point, 10.8 ml. (0.00539 mole) of a 1.5 M solution of 9-borabicyclononane (9-BBN) in tetrahydrofuran was added to the chilled solution (with stirring), and the resulting reaction mixture was then allowed to warm to room temperature (ca. 20°C.) and thereafter stirred for  
20 a period of three days at ambient temperatures. Upon completion of this step, the stirred reaction mixture was next quenched with water, and then partitioned between aqueous 1N hydrochloric acid and methylene chloride, with the two layers thereafter being  
25 separated. The separated aqueous layer was then adjusted to pH 14 with solid sodium hydroxide and thereafter extracted with fresh methylene chloride. The combined organic extracts were subsequently dried over anhydrous sodium sulfate and filtered, and the  
30 resulting filtrate thereafter evaporated to dryness while under reduced pressure to afford a solid residual product. Crystallization of the latter material from isopropanol then gave 334 mg. (22%) of pure cis-3-(cyclohexylmethylamino)-2-benzhydrylquinuclidine as  
35 white crystals melting at 152-153°C. The pure product

was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data, in addition to elemental analysis.

5        Mass Spectrum (%): 389(parent +1, <1.0), 274(3), 222(40), 221(100), 178(25), 165(21), 164(24), 154(44), 110(40), 108(21), 97(25), 96(31), 82(35), 70(21), 56(30), 55(33).

10        NMR Data:  $^1\text{H-NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ ) 0.4-0.6(m, 2H), 1.0-1.2(m, 6H), 1.5-1.7(m, 4H), 1.8-2.0(m, 2H), 2.23(m, 1H), 2.63(t, 1H), 2.7-2.9(m, 4H), 3.18(m, 1H), 3.69(dd, 1H), 4.42(d, 1H), 7.0-7.4(m, 10H).  
13C-NMR ( $\text{CDCl}_3$ ) 20.0, 24.9, 25.5, 25.9, 26.1, 26.6, 30.9, 31.1, 36.9, 42.1, 49.4, 49.6, 55.1, 56.0, 62.0, 126.0, 126.5, 127.5, 128.4, 129.1, 143.2, 145.4.

15        Anal. Calcd. for  $\text{C}_{27}\text{H}_{36}\text{N}_2$ : C, 83.45; H, 9.34; N, 7.21. Found: C, 83.20; H, 9.34; N, 7.21.

#### EXAMPLE 2

The two-step reaction procedure described in Example 1 was repeated except that 2-chlorobenzylamine  
20        was the reagent employed in place of cyclohexylamine, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (yield, 58%), m.p. 172-174°C.

25        Anal. Calcd. for  $\text{C}_{27}\text{H}_{29}\text{ClN}_2$ : C, 77.77; H, 7.01; 6.72. Found: C, 77.34; H, 6.95; N, 6.65.

#### EXAMPLE 3

The two-step reaction procedure described in Example 1 was repeated except that 2-trifluoromethyl-  
30        benzylamine was the reagent employed in place of cyclohexylamine, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-[(2-trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine (yield,  
35        41%), m.p. 164-167°C.

Anal. Calcd. for  $C_{28}H_{29}F_3N_2$ : C, 74.64; H, 6.49; N, 6.22. Found: C, 74.08; H, 6.48; N, 6.06.

#### EXAMPLE 4

The two-step reaction procedure described in Example 1 was repeated except that 2-methoxybenzylamine was the reagent employed in place of cyclohexylamine, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (yield, 71%) m.p. 132-135°C.

Anal. Calcd. for  $C_{28}H_{32}N_2O$ : C, 81.51; H, 7.82; N, 6.79. Found: C, 81.56; H, 7.86; N, 6.68.

#### EXAMPLE 5

The two-step reaction procedure described in Example 1 was repeated prepare the following cis-3-[(cyclic)methylamino]-2-benzhydrylquinuclidines, starting from 3-keto-2-benzhydrylquinuclidine and the appropriate N-(cyclic)methylamine in each instance, and using the same molar proportions as before:

cis-3-[(3-trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 197-199°C.

cis-3-[(4-methoxyphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 154-157°C.

cis-3-[(3-pyridyl)methylamino]-2-benzhydrylquinuclidine, m.p. 130-140°C.

cis-3-[(3,4-dichlorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 182-184°C.

cis-3-[(4-fluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 170-172°C.

cis-3-[(2-pyridyl)methylamino]-2-benzhydrylquinuclidine, m.p. 95-115°C.

cis-3-[(4-pyridyl)methylamino]-2-benzhydrylquinuclidine, m.p. 110-130°C.

cis-3-[(4-chlorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 157-160°C.

cis-3-[(3-methoxyphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 156-158°C.

cis-3-[(2,3-dichlorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 151-154°C.

5     cis-3-[(3-chlorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 186-188°C.

cis-3-[(4-trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 171-173°C.

10     cis-3-[(2-methylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 173-176°C.

cis-3-[(3-methylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 170-174°C.

cis-3-[(4-methylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 175-178°C.

15     cis-3-[(3-fluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 156-159°C.

cis-3-[(4-methoxycarbonylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 175-182°C.

20     cis-3-[(2-fluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 164-166°C.

cis-3-[(2,5-difluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 163-165°C.

cis-3-[(2,6-difluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 154-157°C.

25     cis-3-[(3-methoxycarbonylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 182-185°C.

cis-3-[(3-indolyl)methylamino]-2-benzhydrylquinuclidine, m.p. 207-212°C.

#### EXAMPLE 6

30     A. In a 25 ml. round-bottomed reaction flask equipped with a Dean-Stark trap, reflux condenser and nitrogen-inlet tube, there were placed 505 mg. (0.001405 mole) of 2-[(2,4-dichlorophenyl)phenyl-methyl]quinuclidin-3-one (the product of Preparation B), 225 mg. (0.002107 mole) of benzylamine, 6.5 mg.

35



(0.000028 mole) of camphorsulfonic acid and 7 ml. of toluene. The reaction mixture was then refluxed azeotropically for a period of 18 hours, cooled to ambient temperatures and concentrated in vacuo to afford a solid residue.

B. The solid residual material obtained above (crude 3-benzylimino-2-[(2,4-dichlorophenyl)phenylmethyl]quinuclidine) was next dissolved in 13 ml. of dry tetrahydrofuran, and the resulting solution was cooled to 0°C., with stirring, while under a dry nitrogen atmosphere. At this point, 5.6 ml. (0.002809 mole) of a 0.5M solution of 9-borabicyclononane (9-BBN) in tetrahydrofuran was added to the chilled solution (with stirring), and the resulting reaction mixture was then allowed to warm to room temperature (ca. 20°C.) and thereafter stirred for a period of 24 hours at ambient temperatures. Upon completion of this step, the stirred reaction mixture was next quenched with water, and then partitioned between aqueous 1 N hydrochloric acid and methylene chloride, with the organic layer thereafter being separated. The aqueous phase was then adjusted to pH 14 with solid sodium hydroxide and thereafter extracted with fresh methylene chloride. The combined organic extracts were subsequently dried over anhydrous sodium sulfate and filtered, and the resulting filtrate thereafter evaporated to dryness while under reduced pressure to afford a solid residual product. Crystallization of the latter material from isopropanol then gave 154 mg. (24%) of pure cis-3-benzylamino-2-[(2,4-dichlorophenyl)phenylmethyl]quinuclidine, as white crystals melting at 142-147°C. The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data, in addition to elemental analysis.

Mass Spectrum (%): 451 (parent, 0.5), 216(22), 215(72), 96(21), 91(100).

NMR Data:  $^1\text{H-NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ ) 1.2-2.1 (series of five multiplets, 5H), 2.7-2.8(m, 4H), 3.1-3.3 (m, 2H), 3.6-3.7 (m, 2H), 4.84(d, 1H), 6.7-6.8 and 7.1-7.4(m, 8H).  $^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ) 20.1, 24.6, 25.5, 42.1, 44.1, 49.6, 51.9, 53.8, 62.9, 126.4, 126.8, 127.5, 127.9, 128.2, 128.3, 132.3, 139.8, 139.9, 142.6.

Anal. Calcd. for  $\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_2$ : C, 71.84; H, 6.25; N, 6.21. Found: C, 71.04; H, 6.28; N, 5.63.

#### EXAMPLE 7

The two-step reaction procedure described in Example 6 was repeated except that 2-[(3-methoxyphenyl)phenylmethyl]quinuclidin-3-one (a product of Preparation C) was the reactant employed in place of 2-[(2,4-dichlorophenyl)phenyl-methyl]quinuclidine, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-benzylamino-2-[(3-methoxyphenyl)-phenylmethyl]quinuclidine (yield, 33%), m.p. 80-90°C.

Anal. Calcd. for  $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O} \cdot 0.5\text{H}_2\text{O}$ : C, 79.77,; H, 7.89; N, 6.64. Found: C, 79.36; H, 7.78; N, 6.48.

#### EXAMPLE 8

The two-step reaction procedure described in Example 6 was repeated except that 2-[(4-methoxycarbonylphenyl)phenylmethyl]quinuclidin-3-one (a product of Preparation C) was the reactant employed in place of 2-[(2,4-dichlorophenyl)phenylmethyl]quinuclidine, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-benzylamino-2-[(4-methoxycarbonylphenyl)phenyl-methyl]quinuclidine (yield, 47%), m.p. 156-166°C.

Anal. Calcd. for  $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_2$ : C, 79.06; H, 7.32; N, 6.36. Found: C, 78.80; H, 7.28; N, 6.28.

EXAMPLE 9

The two-step reaction procedure described in Example 6 was repeated to prepare the following cis-3-benzylamino-2-[( $\alpha$ -substituted)phenylmethyl]-quinuclidines, starting from the corresponding 2-[( $\alpha$ -substituted)phenylmethyl]quinuclidin-3-one compounds and benzylamine in each instance, and using the same molar proportions as before:

cis-3-benzylamino-2-[(2,3-dichlorophenyl)-phenylmethyl]quinuclidine, m.p. 150-165°C.

cis-3-benzylamino-2-[(2,4-difluorophenyl)-phenylmethyl]quinuclidine, m.p. 115-140°C.

cis-3-benzylamino-2-[(3-trifluoromethylphenyl)-phenylmethyl]quinuclidine, m.p. 158-160°C.

cis-3-benzylamino-2-[(2-furyl)phenylmethyl]-quinuclidine, m.p. 135-143°C.

cis-3-benzylamino-2-[(3,4-dichlorophenyl)-phenylmethyl]quinuclidine, m.p. 136-139°C.

cis-3-benzylamino-2-[(4-pyridyl)phenylmethyl]-quinuclidine, m.p. 120-135°C.

cis-3-benzylamino-2-[(E- and Z-2-tert.-butylvinyl)-phenylmethyl]quinuclidine, m.p. 85-92°C.

cis-3-benzylamino-2-[(2-methoxyphenyl)phenylmethyl]quinuclidine, m.p. 155-175°C.

cis-3-benzylamino-2-[(2-n-propyl)phenylmethyl]-quinuclidine, m.p. 140-145°C.

cis-3-benzylamino-2-[(4-carboxyphenyl)phenylmethyl]-quinuclidine, m.p. 180°C (decomp.)

cis-3-benzylamino-2-[(2-thienyl)phenylmethyl]-quinuclidine, m.p. 150-163°C.

cis-3-benzylamino-2-[(2-biphenyl)phenylmethyl]-quinuclidine, m.p. 185-195°C.

EXAMPLE 10

The procedure described in Example 6 was repeated to prepare the following cis-3-(2-thienyl)amino-2-[( $\alpha$ -

substituted)phenylmethyl]quinuclidines, starting from the corresponding 2-[( $\alpha$ -substituted)phenylmethyl]-quinuclidin-3-one and 2-thienylamine [which is (2-thienyl)methylamine] in each instance, and using the same molar proportions as before:

cis-3-[(2-thienyl)methylamino]-2-[(2,3-dichlorophenyl)phenylmethyl]quinuclidine, m.p. 129-142°C.

cis-3-[(2-thienyl)methylamino]-2-[(2,4-dichlorophenyl)phenylmethyl]quinuclidine, m.p. 133-138°C.

cis-3-[(2-thienyl)methylamino]-2-[(3-methoxyphenyl)phenylmethyl]quinuclidine, m.p. 105-115°C.

cis-3-[(2-thienyl)methylamino]-2-[(cyclohexyl)phenylmethyl]quinuclidine, m.p. 140-147°C.

cis-3-[(2-thienyl)methylamino]-2-[(3-pyridyl)phenylmethyl]quinuclidine, m.p. 147-153°C.

#### EXAMPLE 11

In a 50 ml. round-bottomed reaction flask equipped with reflux condenser and nitrogen-inlet tube, there were placed 1.022 g. (0.0035 mole) of 3-amino-2-benzhydrylquinuclidine [prepared according to the procedure described by E. J. Warawa et al. in the Journal of Medicinal Chemistry, Vol. 18, p. 71(1975)], 918.7 mg. (0.00525 mole) of 2,6-dichlorobenzaldehyde, 16 mg. of camphorsulfonic acid and 18 ml. of toluene. The resulting reaction mixture was next refluxed for a period of 18 hours azeotropically, and then cooled to room temperature (ca. 20°C.) and evaporated to near dryness while under reduced pressure to afford a solid residue. Crystallization of the latter material from isopropanol then gave 1.32 g. (84%) of pure cis-3-[(2,6-dichlorophenyl)methyleneamino]-2-benzhydrylquinuclidine as a white solid, m.p. 178-182°C.; IR( $\text{cm}^{-1}$ , KBr), 1642(C=N). The pure product was further characterized by means of mass spectrum analysis, and nuclear magnetic resonance data, in addition to

elemental analysis.

Mass Spectrum (%): 427(<1, parent+1), 291(38), 274(21), 260(310), 259(100), 135(21), 96(21), 91(27).

5        NMR Data:  $^1\text{H}$ -NMR( $\delta$ ,  $\text{CDCl}_3$ ) 1.45(m, 1H), 1.81(m, 3H), 2.26(m, 1H), 2.89(m, 1H), 3.08(m, 2H), 3.60(m, 1H), 3.71(m, 1H), 4.01(dd, 2H), 4.68(d, 1H), 7.1-7.5(m, 13H), 7.96(2, 1H),  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) 22.0, 25.4, 31.8, 42.4, 49.5, 50.2, 63.1, 71.3, 125.9, 127.8, 128.2, 128.3, 128.4, 129.3, 130.0, 130.8, 135.5, 143.4, 145.4, 155.8.

10        Anal. Calcd. for  $\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_2$ : C, 72.16; H, 5.83; N, 6.23. Found: C, 71.50; H, 5.79; N, 6.14.

#### EXAMPLE 12

15        The procedure described in Example 11 was repeated except that 2-methoxybenzaldehyde was the reagent employed instead of 2,6-dichlorobenzaldehyde, using the same molar proportions as before. In this particular case, the corresponding final product obtained was cis-3-[(2-methoxyphenyl)methyleneamino]-2-benzhydryl- 20 quinuclidine (yield, 78%), m.p. 157-161°C.

Anal. Calcd. for  $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}$ : C, 81.91; H, 7.36; N, 6.82. Found: C, 81.49; H, 4.76; N, 6.70.

#### EXAMPLE 13

25        The procedure described in Example 11 is followed to prepare the following cis-[3-(homocyclic)methylene-amino]-2-benzhydrylquinuclidines, starting from 3-amino-2-benzhydrylquinuclidine and the appropriate alicyclic or aromatic aldehyde compound in each instance, and using the same molar proportions as 30 before:

cis-3-[(2-carboxyphenyl)methyleneamino]-2-benzhydrylquinuclidine

cis-3-[(cyclopentyl)methyleneamino]-2-benzhydrylquinuclidine

cis-3-[(2-biphenyl)methyleneamino]-2-benzhydrylquinuclidine.

EXAMPLE 14

In a 25 ml. round-bottomed reaction flask equipped with reflux condenser and nitrogen-inlet tube, there were placed 401 mg. (0.000894 mole) of cis-3-[(2,6-dichlorophenyl)methyleneamino]-2-benzhydrylquinuclidine (the product of Example 11) in 4 ml. of dry tetrahydrofuran and 2.2 ml. (0.004471 mole) of a 2.0 M solution of borane-methyl sulfide in tetrahydrofuran. The reaction mixture was next refluxed for a period of five days, then cooled to room temperature (ca. 20°C.) and evaporated to near dryness while under reduced pressure. The solid residue so obtained was next taken up in 5 ml. of ethanol, treated with 500 mg. of solid sodium carbonate and then refluxed for a period of two days. The reaction solution was then cooled to ambient temperatures and thereafter partitioned between ethyl acetate and water, followed by separation of the two layers. The separated ethyl acetate layer was next extracted with 1N aqueous hydrochloric acid and the resulting aqueous acidic layer was thereafter adjusted to pH 10 with solid sodium hydroxide pellets, followed by extraction with methylene chloride. The organic layer thus obtained was then washed with brine and subsequently dried over anhydrous sodium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a solid residue which crystallized from isopropanol to afford 124 mg. (31%) of pure cis-3-[(2,6-dichlorophenyl)methylamino]-2-benzhydrylquinuclidine as a white solid material melting at 155-160°C. The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data, in

addition to elemental analysis.

Mass Spectrum (%): 394(1.4, parent), 289(19), 228(20), 227(100), 158(28), 110(19).

NMR Data:  $^1\text{H-NMR}$ ( $\delta$ ,  $\text{CDCl}_3$ ) 1.38(m, 1H), 1.6-1.8(m, 3H), 2.1-2.2(m, 1H), 2.72(m, 1H), 2.88(m, 2H), 3.15(m, 1H), 3.30(m, 1H), 3.57(m, 1H), 3.82(m, 1H), 3.93(m, 1H), 4.51(3, 1H), 7.0-7.5(m, 13H).  $^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ) 20.1, 25.6, 25.7, 42.1, 47.3, 49.0, 49.6, 56.1, 61.9, 125.9, 126.6, 127.5, 127.6, 128.1, 128.4, 128.6, 129.2, 136.0, 136.1, 142.8, 145.8.

Anal. Calcd. for  $\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_2 \cdot 0.5\text{H}_2\text{O}$ : C, 70.43; H, 6.35; N, 6.08. Found: C, 70.64; H, 6.17; N, 6.08.

#### EXAMPLE 15

The procedure described in Example 11 was repeated to prepare the following cis-3-[(homocyclic)methylamino]-2-benzhydrylquinuclidines, starting from the corresponding cis-3-[(homocyclic)methyleneamino]-2-benzhydrylquinuclidine final products of Example 13 in each instance, and using the same molar proportions as before:

cis-3-[(2-carboxyphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 238-241°C.

cis-3-[(cyclopentyl)methylamino]-2-benzhydrylquinuclidine, m.p. 158-160°C.

cis-3-[(2-biphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 137-143°C.

#### EXAMPLE 16

In a 50 ml. round-bottomed reaction flask equipped with reflux condenser and nitrogen-inlet tube, there were placed 838 mg. (0.002024 mole) of 3-(2-norbornyl-carbonylamino)-2-benzhydrylquinuclidine (the product of Preparation D), 10 ml. of dry tetrahydrofuran and 5.06 ml. (0.010119 mole) of a 2.0 M solution of borane-methyl sulfide in tetrahydrofuran. The reaction mixture was next refluxed for a period of four days,

then cooled to room temperature (ca. 20°C.) and evaporated to near dryness while under reduced pressure. The solid residue so obtained was next taken up in 20 ml. of ethanol, treated with 100 mg. of solid sodium carbonate and then refluxed for a period of 24 hours. The reaction solution was then cooled to ambient temperatures and thereafter partitioned between water and methylene chloride, followed by separation of the two layers. The separated methylene chloride layer was next extracted with 1N aqueous hydrochloric acid, and the resulting aqueous acidic layer was thereafter adjusted to pH 10 with solid sodium hydroxide pellets, followed by extraction again with methylene chloride. The organic layer thus obtained was then washed with brine and subsequently dried over anhydrous sodium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a solid residue which crystallized from isopropanol to give 474 mg. (58%) of pure cis-3-[(2-norbornyl)methylamino]-2-benzhydrylquinuclidine as a white solid melting at 183-189°C. The pure product was further characterized by means of mass spectrum analysis and nuclear magnetic resonance data, in addition to elemental analysis.

Mass Spectrum (%): 401(<1, parent+1), 234(43), 233(100), 176(21), 164(25), 110(29), 67(29).

NMR Data: <sup>1</sup>H-NMR (δ, CDCl<sub>3</sub>) 0.6-3.0 (several multiplets, 22H), 3.27(m, 1H), 3.75(dd, 1H), 4.51(dd, 1H), 7.1-7.5 (10H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 19.9, 20.1, 20.2, 21.9, 22.9, 25.0, 25.1, 25.2, 25.5, 25.6, 28.9, 30.0, 30.1, 35.4, 36.1, 36.6, 36.8, 37.6, 38.6, 38.7, 38.8, 39.3, 39.7, 39.8, 42.1, 42.2, 49.3, 49.5, 49.6, 49.7, 51.4, 51.5, 55.7, 56.9, 57.1, 61.9, 62.0, 126.0, 126.9, 126.6, 127.4, 127.5, 128.4, 129.2, 143.2, 143.4, 145.4.



Anal. Calcd. for  $C_{28}H_{36}N_2 \cdot 0.25H_2O$ : C, 83.02; H, 9.08; N, 6.92. Found: C, 82.98; H, 8.91; N, 6.84.

EXAMPLE 17

5 The procedure described in Example 16 was repeated to prepare the following cis-3-[(homocyclic)methylamino]-2-benzhydrylquinuclidines, starting from the corresponding cis-[(homocyclic)carbonylamino]-2-benzhydrylquinuclidine final products of Preparation E in each instance, and using the same molar proportions as before:

cis-3-[(1-norbornyl)methylamino]-2-benzhydrylquinuclidine, m.p. 173-179°C.

cis-3-[(2-benzylphenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 119-121°C.

15 cis-3-[(3,5-difluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 119-127°C.

cis-3-[(2,3-difluorophenyl)methylamino]-2-benzhydrylquinuclidine, m.p. 148-157°C.

EXAMPLE 18

20 The first part and only this part of the two-step reaction procedure described in Example 1 (i.e., the condensation step) is repeated to prepare the following 3-[(cyclic)methylimino]-2-benzhydrylquinuclidines, starting from 3-keto-2-benzhydrylquinuclidine and the appropriate N-(cyclic)methylamine in each instance, and using the same molar proportions as before, except that this time the desired intermediate product is isolated and purified as such via trituration with isopropanol followed by recrystallization from the same solvent to afford the pure imino compound:

3-(cyclohexylmethylimino)-2-benzhydrylquinuclidine

3-[(2-chlorophenyl)methylimino]-2-benzhydrylquinuclidine

35 3-[(2-trifluoromethylphenyl)methylimino]-2-benzhydrylquinuclidine

3-[(2-methoxyphenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(3-trifluoromethylphenyl)methylimino]-2-  
benzhydrylquinuclidine

5 3-[(4-methoxyphenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(3-pyridyl)methylimino]-2-benzhydryl-  
quinuclidine

10 3-[(3,4-dichlorophenyl)methylimino]-2-benz-  
hydrylquinuclidine

3-[(4-fluorophenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(2-pyridyl)methylimino]-2-benzhydryl-  
quinuclidine

15 3-[(4-pyridyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(4-chlorophenyl)methylimino]-2-benzhydryl-  
quinuclidine

20 3-[(3-methoxyphenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(2,3-dichlorophenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(3-chlorophenyl)methylimino]-2-benzhydryl-  
quinuclidine

25 3-[(4-trifluoromethylphenyl)methylimino]-2-  
benzhydrylquinuclidine

3-[(2-methylphenyl)methylimino]-2-benzhydryl-  
quinuclidine

30 3-[(3-methylphenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(4-methylphenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(3-fluorophenyl)methylimino]-2-benzhydryl-  
quinuclidine

3-[(4-carbomethoxyphenyl)methylimino]-2-benzhydrylquinuclidine

3-[(2-fluorophenyl)methylimino]-2-benzhydrylquinuclidine

5 3-[(2,5-difluorophenyl)methylimino]-2-benzhydrylquinuclidine

3-[(2,6-difluorophenyl)methylimino]-2-benzhydrylquinuclidine

10 3-[(3-methoxycarbonylphenyl)methylimino]-2-benzhydrylquinuclidine

3-[(3-indolyl)methylimino]-2-benzhydrylquinuclidine

3-[(2-norbornyl)methylimino]-2-benzhydrylquinuclidine

15 3-[(1-norbornyl)methylimino]-2-benzhydrylquinuclidine

3-[(2-benzylphenyl)methylimino]-2-benzhydrylquinuclidine

20 3-[(3,5-difluorophenyl)methylimino]-2-benzhydrylquinuclidine

3-[(2,3-difluorophenyl)-2-benzhydrylquinuclidine.

#### EXAMPLE 19

The first part and only this part of the two-step reaction procedure described in Example 6 (i.e., the  
25 condensation step) is repeated to prepare the following 3-benzylimino-2-[( $\alpha$ -substituted)phenylmethyl]quinuclidines, starting from the corresponding 2-[( $\alpha$ -substituted)phenylmethyl]quinuclidin-3-one compounds (products of Preparations B-C) and benzylamine in each  
30 instance, and using the same molar proportions as before, except that this time the desired intermediate product is isolated and purified as such via trituration with isopropanol followed by recrystallization from the same solvent to afford the  
35 pure imino compound:

- 3-benzylimino-2-[(2,4-dichlorophenyl)phenylmethyl]-  
quinuclidine
- 3-benzylimino-2-[(3-methoxyphenyl)phenylmethyl]-  
quinuclidine
- 5 3-benzylimino-2-[(4-methoxycarbonylphenyl)phenyl-  
methyl]quinuclidine
- 3-benzylamino-2-[(2,3-dichlorophenyl)phenylmethyl]-  
quinuclidine
- 10 3-benzylamino-2-[(2,4-difluorophenyl)phenylmethyl]-  
quinuclidine
- 3-benzylamino-2-[(3-trifluoromethylphenyl)phenyl-  
methyl]quinuclidine
- 3-benzylamino-2-[(2-furyl)phenylmethyl]quinuclidine
- 3-benzylamino-2-[(3,4-dichlorophenyl)phenylmethyl]-  
quinuclidine
- 15 3-benzylamino-2-[(4-pyridyl)phenylmethyl]quinuclidine
- 3-benzylamino-2-[(E- and Z-2-tert.-butylvinyl)phenyl-  
methyl]quinuclidine
- 3-benzylamino-2-[(2-methoxyphenyl)phenylmethyl]-  
quinuclidine
- 20 3-benzylamino-2-[(2-n-propyl)phenylmethyl]-  
quinuclidine
- 3-benzylamino-2-[(4-carboxyphenyl)phenylmethyl]-  
quinuclidine
- 25 3-benzylamino-2-[(2-thienyl)phenylmethyl]quinuclidine
- 3-benzylamino-2-[(2-biphenyl)phenylmethyl]-  
quinuclidine.

#### EXAMPLE 20

- The procedure described in Example 6 is repeated  
to prepare the following 3-[(2-thienyl)methylimino]-2-  
[( $\alpha$ -substituted)phenylmethyl]quinuclidines, starting  
from the corresponding 2-[( $\alpha$ -substituted)phenylmethyl]-  
quinuclidin-3-one and (2-thienyl)methylamine (i.e.,  
2-thenylamine) in each instance, and using the same  
35 molar proportions as before except that this time the

desired intermediate product is isolated as such via trituration with isopropanol followed by recrystallization from the same solvent to afford the pure imino compound:

5 3-[(2-thienyl)methylimino]-2-[(2,3-dichloro-  
phenyl)phenylmethyl]quinuclidine

3-[(2-thienyl)methylimino]-2-[(2,4-dichloro-phenyl)phenylmethyl]quinuclidine

3-[(2-thienyl)methylimino]-2-[(3-methoxy-  
10 phenyl)phenylmethyl]quinuclidine

3-[(2-thienyl)methylimino]-2-[(cyclohexyl)-phenylmethyl]quinuclidine

3-[(2-thienyl)methylimino]-2-[(3-pyridyl)-phenylmethyl]quinuclidine.

15 Example 21

The procedure described in Example 11 is followed to prepare the following cis-3-[(cyclic)methylene-amino]-2-benzhydrylquinuclidines, starting from 3-amino-2-benzhydrylquinuclidine and the appropriate cyclic aldehyde compound in each instance, and using the same molar proportions as before:

cis-3-(cyclohexylmethyleamino)-2-benzhydryl-  
quinuclidine

25      cis-3-[(2-chlorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(2-trifluoromethylphenyl)methyleneamino]-2-benzhydrylquinuclidine

cis-3-[(3-trifluoromethylphenyl)methyleneamino]-2-benzhydrylquinuclidine

30            cis-3-[(4-methoxyphenyl)methyleneamino]-2-benz-  
              hydrylquinuclidine

cis-3-[(3-pyridyl)methyleneamino]-2-benzhydryl-  
quinuclidine

35 cis-3-[(3,4-dichlorophenyl)methyleneamino]-2-benzhydrylquinuclidine

cis-3-[(4-fluorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(2-pyridyl)methyleneamino]-2-benzhydryl-  
quinuclidine

5     cis-3-[(4-pyridyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(4-chlorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

10     cis-3-[(3-methoxyphenyl)methyleneamino]-2-benz-  
hydrylquinuclidine

cis-3-[(2,3-dichlorophenyl)methyleneamino]-2-benz-  
hydrylquinuclidine

cis-3-[(3-chlorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

15     cis-3-[(4-trifluoromethylphenyl)methyleneamino]-2-  
benzhydrylquinuclidine

cis-3-[(2-methylphenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

20     cis-3-[(3-methylphenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(4-methylphenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(3-fluorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

25     cis-3-[(4-methoxycarbonylphenyl)methyleneamino]-2-  
benzhydrylquinuclidine

cis-3-[(2-fluorophenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

30     cis-3-[(2,5-difluorophenyl)methyleneamino]-2-benz-  
hydrylquinuclidine

cis-3-[(2,6-difluorophenyl)methyleneamino]-2-benz-  
hydrylquinuclidine

cis-3-[(3-methoxycarbonylphenyl)methyleneamino]-2-  
benzhydrylquinuclidine

cis-3-[(3-indolyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(2-norbornyl)methyleneamino]-2-benzhydryl-  
quinuclidine

5      cis-3-[(1-norbornyl)methyleneamino]-2-benzhydryl-  
quinuclidine

cis-3-[(2-benzylphenyl)methyleneamino]-2-benzhydryl-  
quinuclidine

10      cis-3-[(3,5-difluorophenyl)methyleneamino]-2-benz-  
hydrylquinuclidine

cis-3-[(2,3-difluorophenyl)methyleneamino]-2-benz-  
hydrylquinuclidine.

#### EXAMPLE 22

15      The quinuclidine compounds of the present  
invention are tested for substance P antagonist  
activity in bovine caudate tissue, using a modification  
of the standard assay procedure described by M. A.  
Cascieri et al., as reported in the Journal of  
Biological Chemistry, Vol. 258, p. 5158 (1983).

20      In this procedure, bovine caudate tissue is  
removed from a -70°C. freezer and homogenized in 50  
volumes (w./v.) of ice-cold 50 mM Tris (i.e.,  
tromethamine which is 2-amino-2-hydroxymethyl-1,3-  
propanediol) hydrochloride buffer having a pH of 7.7.  
25      The homogenate is centrifuged at 30,000 x G for a  
period of 20 minutes. The pellet is resuspended in 50  
volumes of Tris buffer, rehomogenized and then  
recentrifuged at 30,000 x G for another twenty-minute  
period. The pellet is then resuspended in 40 volumes  
30      of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM  
of calcium chloride, 2 mM of magnesium chloride, 40 µg.  
/ml. of bacitracin, 4 µg./ml. of leupeptin, 2 µg. of  
chymostatin and 200 µg./ml. of bovine serum albumin.  
This step completes the production of the tissue  
35      preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100  $\mu$ l. of the test compound made up to a concentration of 1  $\mu$ M, followed by the addition of 100  $\mu$ l. of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800  $\mu$ l. of the tissue preparation produced as described above. The final volume is thus 1.0 ml., and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C.) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC<sub>50</sub> values are calculated by using standard statistical methods.

#### EXAMPLE 23

The following cis-[(cyclic)methylamino]-2-benzhydrylquinuclidine final products of Examples 2, 3 and 4, respectively, were tested for anti-inflammatory activity in rats, using the standard rat foot edema test, according to the general procedure described by C. A. Winter et al., as first reported in the Proceedings of the Society for Experimental Biology and Medicine, Vol. 111, p. 544 (1962). The compounds were administered orally (by gavage) at 32 mg./kg. and the results obtained are reported below in terms of the percent (%) inhibition of edema formation afforded by each test compound as compared to the control (i.e.,

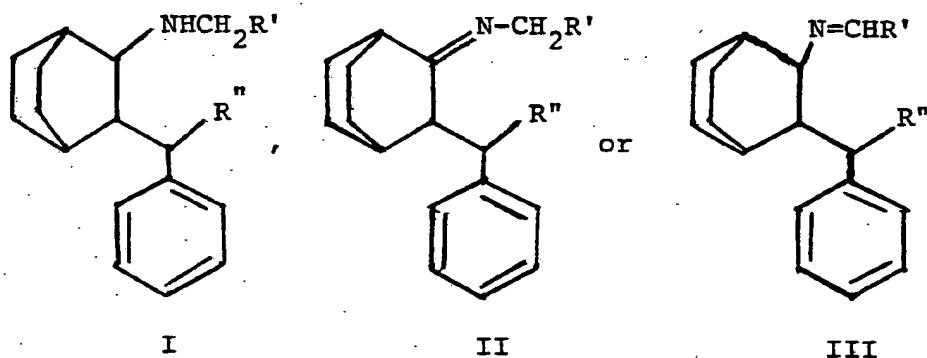


vehicle alone with no compound):

| <u>Compound</u>      | <u>%Inhibition<br/>at 32 mg./kg.</u> |
|----------------------|--------------------------------------|
| Product of Example 2 | 29                                   |
| Product of Example 3 | 50                                   |
| Product of Example 4 | 38                                   |

CLAIMS

1. A compound selected from quinuclidine derivatives of the formula:



or a pharmaceutically acceptable salt thereof, wherein

R' is cycloalkyl having from five to seven carbon atoms, norbornyl, pyrrolyl, thienyl, pyridyl, indolyl, biphenyl or phenyl optionally substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbons in the alkoxy moiety or benzyloxycarbonyl; and

R'' is branched chain alkyl having from three to four carbon atoms, branched chain alkenyl having from five to six carbon atoms, cycloalkyl having from five to seven carbon atoms, furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety or

benzyloxycarbonyl, with the proviso that said R" is other than unsubstituted phenyl when said R' is unsubstituted phenyl, pyrrolyl or thienyl.

2. A compound as claimed in claim 1 of the formula I having the cis-configuration.

3. A compound as claimed in claim 1 of the formula II.

4. A compound as claimed in claim 1 of the formula III having the cis-configuration.

5. A compound as claimed in claim 3 wherein R' is 2-chlorophenyl and R" is phenyl.

6. A compound as claimed in claim 3 wherein R' is 2-trifluoromethylphenyl and R" is phenyl.

7. A compound as claimed in claim 3 wherein R' is 2-methoxyphenyl and R" is phenyl.

8. A compound as claimed in claim 4 wherein R' is 2-chlorophenyl and R" is phenyl.

9. A compound as claimed in claim 4 wherein R' is 2-trifluoromethylphenyl and R" is phenyl.

10. A compound as claimed in claim 4 wherein R' is 2-methoxyphenyl and R" is phenyl.

11. A compound as claimed in claim 2 wherein R" is substituted phenyl.

12. A compound as claimed in claim 11 wherein R' is phenyl or 2-thienyl.

13. A compound as claimed in claim 12 wherein R" is 3-methoxyphenyl.

14. A compound as claimed in claim 12 wherein R' is phenyl and R" is 4-methoxycarbonylphenyl.

15. A compound as claimed in claim 2 wherein R" is furyl or pyridyl.

16. A compound as claimed in claim 2 wherein R" is unsubstituted phenyl.

17. A compound as claimed in claim 16 wherein R' is pyridyl or indolyl.

18. A compound as claimed in claim 17 wherein R' is 4-pyridyl.

19. A compound as claimed in claim 17 wherein R' is 3-indolyl.

20. A compound as claimed in claim 16 wherein R' is substituted phenyl.

21. A compound as claimed in claim 20 wherein R' is fluorophenyl, difluorophenyl or chlorophenyl.

22. A compound as claimed in claim 21 wherein R' is 2-chlorophenyl.

23. A compound as claimed in claim 20 wherein R' is trifluoromethylphenyl.

24. A compound as claimed in claim 23 wherein R' is 2-trifluoromethylphenyl.

25. A compound as claimed in claim 20 wherein R' is alkylphenyl or alkoxyphenyl.

26. A compound as claimed in claim 25 wherein R' is 4-methylphenyl.

27. A compound as claimed in claim 25 wherein R' is 2-methoxyphenyl.

28. A compound as claimed in claim 20 wherein R' is alkoxycarbonylphenyl.

29. A compound as claimed in claim 28 wherein R' is 4-methoxycarbonylphenyl.

30. cis-3-[(2-Chlorophenyl)methylamino]-2-benzhydrylquinuclidine.

31. cis-3-[(2-Trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine.

32. cis-3-[(2-Methoxyphenyl)methylamino]-2-benzhydrylquinuclidine.

33. A pharmaceutical composition useful for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in mammals, comprising a pharmaceutically acceptable carrier or diluent and a therapeutically-

effective amount of a compound as claimed in claim 1.

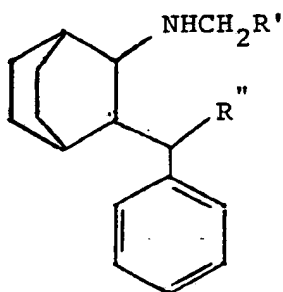
34. The composition according to claim 33 wherein the compound is of the formula I wherein R' is 2-chlorophenyl and R" is phenyl.

35. The composition according to claim 33 wherein the compound is of the formula I wherein R' is 2-trifluoromethylphenyl and R" is phenyl.

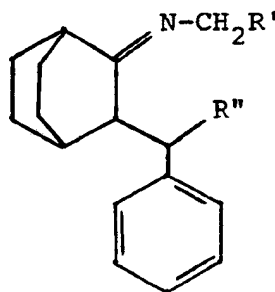
36. The composition according to claim 33 wherein the compound is of the formula I wherein R' is 2-methoxyphenyl and R" is phenyl.

37. A pharmaceutical composition useful for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment, comprising a pharmaceutically acceptable carrier or diluent and an amount of a compound as claimed in claim 1 that is effective for antagonizing the effects of substance P at its receptor site in said mammal.

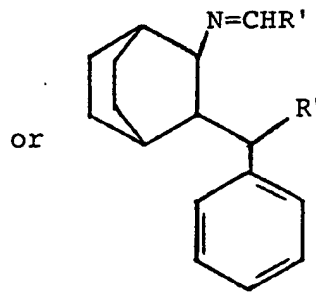
38. A method of treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment, which comprises administering to said mammal a therapeutically-effective amount of a compound selected from quinuclidine derivatives of the formula:



# I



II



III

or a pharmaceutically acceptable salt thereof, wherein

R' is cycloalkyl having from five to seven carbon atoms, norbornyl, pyrrolyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbons in the alkoxy moiety or benzyloxycarbonyl; and

R'' is branched chain alkyl having from three to four carbon atoms, branched chain alkenyl having from five to six carbon atoms, cycloalkyl having from five to seven carbon atoms, furyl, thienyl, pyridyl, indolyl, biphenyl or phenyl optionally substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety or benzyloxycarbonyl.

39. The method as claimed in claim 38 wherein said compound administered is of the formula I.

40. The method as claimed in claim 38 wherein said compound administered is of the formula II.

41. The method as claimed in claim 38 wherein said compound administered is of the formula III.

42. The method as claimed in claim 41 wherein said compound administered is cis-3-[(2-chlorophenyl)-methylamino]-2-benzhydrylquinuclidine.

43. The method as claimed in claim 41 wherein said compound administered is cis-3-[(2-trifluoromethylphenyl)methylamino]-2-benzhydrylquinuclidine.

44. The method as claimed in claim 41 wherein said compound administered is cis-3-[(2-methoxyphenyl)-

methylamino]-2-benzhydrylquinuclidine.

45. The method as claimed in claim 41 wherein said compound administered is cis-[(2-thienyl)methylamino]-2-benzhydrylquinuclidine.

46. A method for antagonizing substance P in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine in a mammal in need of such treatment, which comprises administering to said mammal a compound as claimed in claim 38 in an amount that is effective for antagonizing the effects of substance P at its receptor site in said mammal.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/04205

|   |   |                                     |
|---|---|-------------------------------------|
| <b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>   |   |                                     |
| According to International Patent Classification (IPC) or to both National Classification and IPC   |   |                                     |
| IPC(4): A61K 31/445; C07D 453/02  |   |                                     |
| U.S.Cl.: 514/133; 546/133   |   |                                     |
| <b>II. FIELDS SEARCHED</b>  |   |                                     |
| Minimum Documentation Searched <sup>7</sup>   |   |                                     |
| Classification System   | Classification Symbols  |                                     |
| U.S.  | 514/133; 546/133  |                                     |
| Documentation Searched other than Minimum Documentation<br>to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>   |   |                                     |
|   |   |                                     |
| <b>DARC-QUESTEL ONLINE SUBSTRUCTURE SEARCH</b>  |   |                                     |
| <b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>  |   |                                     |
| Category <sup>a</sup>   | Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>  | Relevant to Claim No. <sup>13</sup> |
| A   | U.S. , A, 3,560,510 (WARAWA) 2 February 1971, see formula III.  | 1-46                                |
| Y   | U.S. A, 3,864,385 (FEIT ET AL) 4 February 1975, see column 1, lines 45 to 47.   | 1,2,11,<br>12,33,37                 |
| Y   | U.S., A, 3,933,906 (WERNER) 20 January 1976, see column 3, lines 4 to 15.   | 1,2,11,<br>12,33,37                 |
| Y   | Journal of Medicinal Chemistry, Volume 18, No. 6 (1975), pages 587 to 593, E. WARAWA. ET AL. "Quinuclidine Chemistry. 4. Diuretic Properties of Cis 3-amino-2-benzhydryl-quinuclidine". See formula 11, page 587. | 1,2,11,<br>12,33,37                 |
| <p><sup>a</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> |   |                                     |
| <b>IV. CERTIFICATION</b>  |   |                                     |
| Date of the Actual Completion of the International Search   | Date of Mailing of this International Search Report   |                                     |
| 9 JANUARY 1989  | 01 MAR 1989   |                                     |
| International Searching Authority   | Signature of Authorized Officer   |                                     |
| ISA/US  | RICHARD A. SCHWARTZ   |                                     |